DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date November 20, 1997

From Acting Director, Division of Health Effects Evaluation, HFS-225

Subject FAP 4M4428; Further Evaluation of Toxicological Studies

To Memorandum to the File

In reviewing the petition to approve the use of radiation to treat red meat, we have considered additional relevant information in our files. This includes a large number of animal feeding studies and genetic toxicity studies that were part of a review fifteen years ago. While still acknowledging that not all of the individual study reports can stand alone to provide definitive answers, the present analysis has built on the earlier evaluation of individual studies to consider the overall weight of evidence resulting from studies with appropriate design and execution. Taken together, these studies present a consistent finding of no harm when irradiated flesh foods (i.e., red meat, chicken, and fish) were tested in animal feeding studies and genetic toxicity studies. The discussion below summarizes the earlier review and elaborates on how the current evaluation of all the data taken together allows us to draw a broader conclusion on safety than reached previously.

In 1979, in light of international developments regarding safety evaluations of irradiated foods, FDA's Bureau of Foods established the Bureau of Foods Irradiated Foods Committee (BFIFC) to reassess the criteria for evaluating the potential toxicity resulting from applying radiation to foods. In 1980, BFIFC concluded that substances known to be formed in food because of radiation were the same as, or chemically similar to, components found in foods that have not been irradiated and that under expected irradiation conditions these radiolytic products would be formed in low concentrations. BFIFC concluded that in certain cases (for those foods irradiated at a low dose or consumed in small amounts), irradiating a food raised no toxicological concern and animal feeding studies were not necessary to demonstrate safety. They further recommended, however, that foods irradiated at doses above 1 kGy and consumed in significant amounts warrant toxicological evaluation.

Subsequently, in 1981, the Bureau of Foods established the Task Group for the Review of Toxicology Data on Irradiated Foods to determine whether toxicology data available to the agency were sufficient to conclude that all irradiated foods were toxicologically safe, or whether any patterns in the data would raise toxicological concern. The Task Group identified all data that might be relevant to toxicological safety. They designed data forms to summarize the important features of the reports reviewed and categorized available reports according to whether they met contemporary standards, whether they appeared to be of good quality but provided insufficient information to stand alone to assess safety, or whether they were critically flawed and could not be used to assess safety. The Task Group concentrated on carcinogenicity and reproduction studies that met 1980's standards and studies that reported effects that could be of toxicological concern.

They did not attempt to obtain additional data on studies that showed no effects but were incompletely reported or on studies that presented issues needing further evaluation[1]. Given the fact that the group was charged to review all data and issue a prompt report, it is not surprising that they concentrated on what conclusions could be drawn from individual studies. Application of a wide body of data, taken as a whole, to a safety assessment on all whole foods would have required a novel approach for which there was little precedent.

After approximately six months of intensive effort, the Task Group concluded that studies with irradiated foods do not appear to show adverse effects. However, the memorandum also concluded that "(S)tudies of sufficiently high quality to support the safety of irradiated foods treated at high radiation doses which constitute major contributions to the daily diet for long-term use are also not available". It is important to consider this statement in context and in light of what has been learned since that time.

First, it is important to recognize that the animal feeding studies conducted on whole foods are best described as "wholesomeness" studies, which attempt to demonstrate that a food supports healthy growth without adverse effects. These differ from classical toxicology studies which, to characterize toxic potential most thoroughly, are generally designed to elicit toxicity, at least, in the highest dose. An acceptable food eaten in appropriate amounts in a nutritionally balanced diet should generally not elicit toxicity at any dose.

In wholesomeness studies it is particularly difficult to incorporate as much of the test article into the diet as desirable to magnify the power to detect a toxic effect without distorting the diet so much as to produce nutritional imbalance. The Task Group for the Review of Toxicology Data on Irradiated Foods final report of April 9, 1982, recognized that it would be difficult to devise a toxicology study of an irradiated whole food that would have the sensitivity normally expected for traditional toxicity testing. Another way of looking at this difficulty is that it is extremely unlikely that radiolytic products will be present in amounts sufficiently high to elicit toxicity when the irradiated food is fed in amounts that an animal can consume in a nutritionally adequate diet.

Second, the large number of studies and the various reporting approaches made it very difficult, at times, for individual reviewers on the Task Group to evaluate all relevant data from a given study. Specifically, we have noted that different aspects of some studies were discussed in separate reports and considered by the Task Group as independent, incompletely reported studies. On some of these occasions, the authors of the different parts were different, presumably because different members of the team conducting the research would have been responsible for different parts of the research and may have reported their findings separately. For example, a

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[1] FDA later obtained additional data and gave further consideration to three studies on irradiated poultry, resolving concerns that caused the Task Group to find these studies less than fully acceptable.

report by Thompson and Hunt (351A) is simply a histopathology analysis for a study by Read *et al.*(291A). In another case, a study by Monsen (233) raised serious concerns that were later demonstrated to be unrelated to irradiation in a replicate study by Thompson (352) and that were further explained in follow up studies reported in a congressional hearing July 18 and 30, 1968. In our reanalysis, we have seen several examples where reports analyzed individually by different reviewers relate to the same study and can provide more valuable information when reviewed together.

In other cases, the research was designed to study several different irradiated foods simultaneously, in one or more animal species, and the experimental findings from each of the irradiated foods were described in the same report. Such complex reports made detailed analysis in a short time frame difficult when the same reviewer was responsible for evaluating several reports and tended to mask recognition of how many studies showing no effects were actually conducted. One significant advantage we have today is the enhanced ease in assembling the important factors from the large number of studies in a computerized database and to display such information on spreadsheets. The present analysis benefits from such assembling of the data beyond that which was done in 1982. When the results of all the studies are displayed this way, the striking consistency of negative toxicity findings becomes more obvious. Additionally, the rare observation that merits further consideration can be viewed and analyzed in the context of similar studies.

One confounding factor results from the fact that many of the early studies, which were conducted by highly competent scientists in the government or academia, were conducted at a time when testing and reporting protocols were not standardized to the extent expected when the Task Group was reviewing the data. Animal group sizes were often smaller, the parameters measured were sometimes different, and the extent of histopathology conducted was sometimes less than expected today. Also, there appears to have been less emphasis on providing detailed documentation for negative results. This does not mean that the studies were not well-conducted or that they did not provide substantial safety information. While total histopathology may not have been reported for all studies, it was performed for many with a consistent absence of toxicologically significant findings.

In sum, the present analysis represents a weight of evidence evaluation based on the entire record as interpreted by expert judgement. Such an approach is entirely sound considering: (1) a data base as large as that evaluated here and (2) the absence of any specific reason to suspect toxicity under the conditions of use. While there are sporadically manifested indications of differences in measured parameters, there is an absence of toxicological effects attributable to irradiation of foods. This large collection of studies without toxicity provides strong evidence for the safety of irradiated foods.

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cc: HFS-200 (Rulis); HFS-205 (Pauli, Tarantino); HFS-215 (Coleman, Lipman); HFS-225(Hattan, Biddle; Irausquin); HFS-235 (Cebula); HFS-245 (Diachenko, Kuznesof)